

'That's the reason they're called lessons', the Gryphon remarked: 'because they lessen from day to day.'

Lewis Carroll, Alice in Wonderland

This issue of **Bandolier** focuses on lessons re-learned, and lessons, moreover, that do not lessen from day to day. We have learnt that studies that are not randomised over-estimate the effects of treatment, and those studies that are not double blind over estimate the effects of treatment (**Bandolier** 17). Many times we find examples of this. This month we find two further pertinent examples.

One looked at interventions to reduce teenage pregnancies. It showed that observational studies found interventions to be successful. Randomised studies showed that they were not. The other looked at cisapride for non ulcer dyspepsia. A single large open study found fantastic efficacy with cisapride, though the placebo group was in line with that from double blind trials. The result of combining all studies was that the effect of cisapride was over-estimated by a substantial amount.

Information strategy

Another lesson is about the need for tools. 'Give us the tools, and we will finish the job' said Winston Churchill. We need rapid access to knowledge. Yet a survey in primary care in the Northern & Yorkshire Region [1] showed only 22% of GPs had good access to electronic information in their practice. Other health professionals were way down the line.

Bandolier has its own solution. Buy an iMac for the practice. Buy Microsoft Office because it has Explorer. Buy the book reviewed on page 5 with all the Internet sites you'd ever want. Take out a subscription to the Cochrane Library on-line, with about 800 reviews, 250,000 controlled trials, and much more. All this and still with change out of £1000 if you shop around. It's called an information strategy.

Professionals (and patients and the public for that matter), should be throwing tantrums: 'We want it now!'. That should apply to infotech, and to better knowledge about products. Try seeing all reps for one week, and saying that you will see them next when they have a systematic review of the product they are promoting. Quiet times ahead for you, headless chicken times at corporate HQ. But apply the tantrum information strategy to PCGs and Health Authorities as well.

Reference:

- 1 Access to the evidence base from general practice in Northern and Yorkshire region. NHS Centre for Reviews and Dissemination.

PREVENTING TEENAGE PREGNANCY

If you were set the task of designing a programme to prevent teenage pregnancies, where would you start? Most of us would now start with a search for a systematic review on the subject. But suppose that review included both randomised and observational studies: would it make a difference?

A scintillating examination of this question [1] comes up with a straight, if hard, answer. Observational studies conclude that interventions work. Randomised trials demonstrate that they do not.

Search

Eleven computerised databases were searched, eight journals hand searched, and reference lists reviewed of all relevant papers. Included were randomised and observational studies on adolescents 18 years or less and evaluating primary prevention programmes with outcomes of start of sexual intercourse, birth control use or responsible sexual behaviour.

Results

There were 25 key reports with 30 studies; 13 were randomised and 17 were observational. Of the 25 reports, 13 were published in journals, three were chapters in textbooks, six were doctoral theses, one a masters thesis and two were unpublished.

For females, observational studies had statistically significant results for intervention over control for all four outcomes (Table). Randomised studies were not significantly different for any outcome.

For males, observational studies had statistically significant results for intervention over control for two of four out-

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*The views expressed in **Bandolier** are those of the authors, and are not necessarily those of the NHSE*

Table: Interventions for adolescent pregnancy prevention - randomised versus observational studies

	Odds ratio (intervention versus control; 95% CI)			
	Starting intercourse	Pregnancy	Responsible sexual behaviour	Birth control use
Females				
Randomised trials (N 7-9)	1.1 (0.90 to 1.32)	1.1 (0.91 to 1.27)	1.0 (0.75 to 1.36)	1.0 (0.64 to 1.54)
Observational studies (N 6-11)	0.64 (0.44 to 0.93)	0.74 (0.56 to 0.98)	1.3 (1.1 to 1.5)	1.4 (1.2 to 1.6)
Males				
Randomised trials (N 3-4)	0.81 (0.35 to 1.90)	0.97 (0.62 to 1.51)	0.94 (0.55 to 1.60)	0.91 (0.71 to 1.18)
Observational studies (N 2-6)	0.71 (0.52 to 0.98)	0.85 (0.68 to 1.06)	1.2 (1.04 to 1.4)	0.82 (0.35 to 1.91)

For starting intercourse and pregnancy, odd ratios less than 1 indicate a desirable effect of intervention. For responsible sexual behaviour and birth control use odds ratios greater than 1 indicate a desirable effect of intervention. Shaded results are statistically better than control. N indicates number of trials included in analysis.

comes (Table). Randomised studies were not significantly different for any outcome.

Comment

There are at least three important lessons in this paper.

For those interested in reducing teenage pregnancy the message is bleak. The highest quality studies show that interventions do not work. Perhaps a really clever person might dredge some comfort from individual studies, but it is hard to see where that comfort will come from.

Yet again we learn the hard lesson that randomisation is everything. One example as to why observational studies were positive is given in the paper, where investigators assigned adolescents declining participation in the intervention group to the control group. It is entirely likely that adolescents receiving the intervention were more receptive to the message, and those in the control group were not. Magically statistical significance results from people doing much as they would have done anyway. The lesson is that including observational studies in reviews may lead us to make policy based on incorrect assumptions. "One of these [2] received wide public attention in the United Kingdom and was considered key data for public health policy".

The final lesson is about the amount of unpublished material. Only 13 of the 25 reports were in journals. Many were as dissertations, even the RCTs, and some were not small. This is good evidence that, in some areas at least, unpublished material might be important. *Bandolier* found it more convincing than a ramble through the publication bias literature [3].

Reference:

- 1 GH Guyatt et al. Randomized trials versus observational studies in adolescent pregnancy prevention. *Journal of Clinical Epidemiology* 2000 53: 167-174.
- 2 R Dickson et al. Preventing and reducing the adverse effects of unintended teenage pregnancies. *Effective Health Care* 1997 3: 1-12.
- 3 A Thornton, P Lee. Publication bias in meta-analysis: its causes and consequences. *Journal of Clinical Epidemiology* 2000 53: 207-216.

CISAPRIDE FOR NON-ULCER DYSPEPSIA

Cisapride is a prokinetic drug that enhances gastrointestinal motility and increases the lower oesophageal sphincter tone, thereby minimising gastrooesophageal reflux. Gastric and duodenal emptying are enhanced because of increased gastric and duodenal contractility and coordination.

A systematic review [1] not only serves to help us understand the effectiveness of this compound, not much used in the UK, but also is a useful example of why we choose high quality studies for decision making.

Search

Six electronic databases were searched, including the Cochrane library, and manufacturers contacted about unpublished studies. Participants were adult patients with a diagnosis of non-ulcer dyspepsia. Oesophagitis, gastric or duodenal ulcer and gastric erosion as causes of dyspepsia were eliminated by endoscopy.

Studies included had to be randomised comparisons of cisapride with placebo or a control treatment. The main outcome was the number of patients experiencing either excellent, or excellent and good improvement of symptoms.

Results

There were 16 studies included, with 902 patients given cisapride and 664 patients given placebo. Two were open studies, and 14 were double blind. The dose of cisapride varied between 15 and 40 mg daily, but in most the dose was 20 mg three times a day. The duration of studies was two to six weeks, but most were over three or four weeks.

There were major differences between the two open studies and those that were double blind (Table). The outcome of excellent symptom improvement was obtained by 129/371 patients (35%) given cisapride and 54/377 (14%) of

Table: Results for cisapride in non ulcer dyspepsia according to outcome (excellent, or good or excellent symptom improvement) and by open and double blind design

Excellent response with:					
Design	Number of trials	Cisapride (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
Open, randomised	2	277/426 (65)	26/181 (15)	4.4 (3.1 to 6.3)	2.0 (1.7 to 2.3)
Double blind, randomised	11	129/371 (35)	54/377 (14)	2.4 (1.8 to 3.2)	4.9 (3.8 to 6.9)
All trials	13	406/797 (51)	80/558 (14)	3.2 (2.6 to 4.0)	2.7 (2.4 to 3.1)

Good or excellent response with:					
Design	Number of trials	Cisapride (%)	Placebo (%)	Relative benefit (95% CI)	NNT (95% CI)
Open, randomised	2	393/426 (92)	80/181 (44)	2.1 (1.8 to 2.5)	2.1 (1.8 to 2.5)
Double blind, randomised	14	323/476 (68)	207/483 (43)	1.6 (1.4 to 1.8)	4.0 (3.2 to 5.3)
All trials	16	716/902 (79)	287/664 (43)	1.8 (1.6 to 2.0)	2.8 (2.5 to 3.2)

those given placebo in double blind studies (Figure 1). The NNT was 4.9 (95% confidence interval 3.8 to 6.9). This was significantly higher (worse) than the NNT of 2.0 for the two open studies and 2.7 for all studies combined.

The outcome of good or excellent symptom improvement was obtained by 323 / 476 patients (68%) given cisapride and 207 / 483 (43%) of those given placebo in double blind stud-

ies (Figure 2). The NNT was 4.0 (95% confidence interval 3.2 to 5.3). This was significantly higher (worse) than the NNT of 2.1 for the two open studies and 2.8 for all studies combined.

In addition, three studies compared cisapride 20 or 30 mg a day with ranitidine 300 mg a day, cimetidine 800 mg a day and nizatidine 300 mg a day. Combining these three trials,

Figure 1: Individual trials with cisapride with excellent symptom improvement. Shaded symbols are open studies.

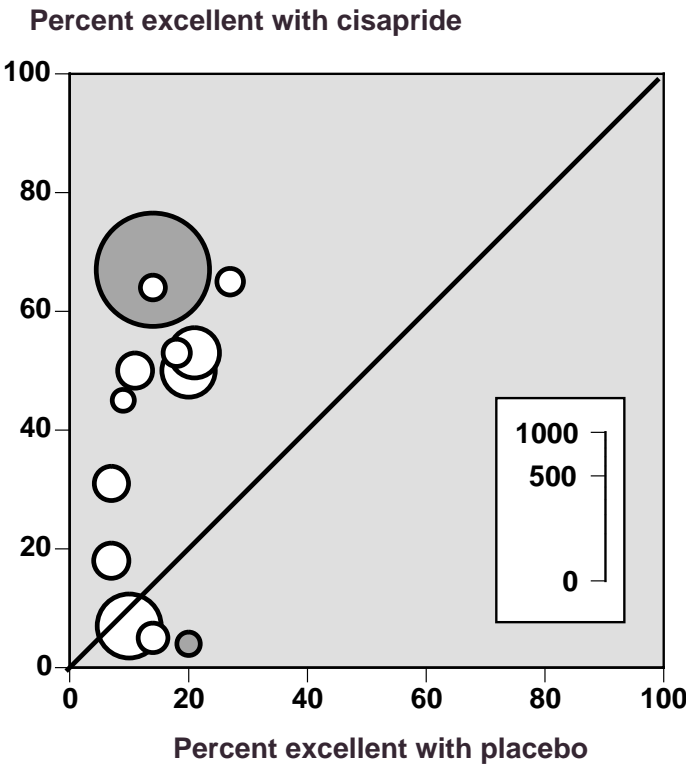


Figure 2: Individual trials with cisapride with good or excellent symptom improvement. Shaded symbols are open studies.

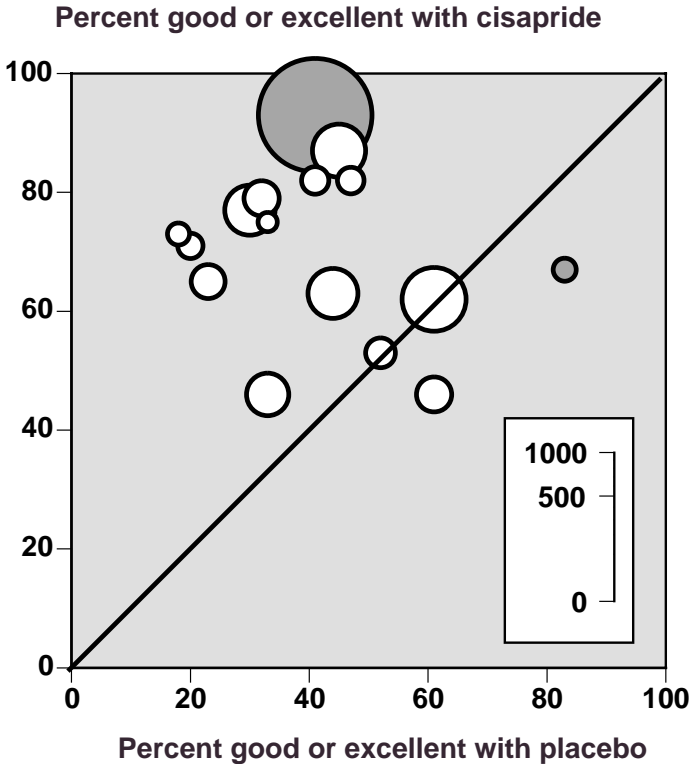


Figure 3: Placebo response rates in individual trials with cisapride with excellent symptom improvement. Shaded symbols are open studies.

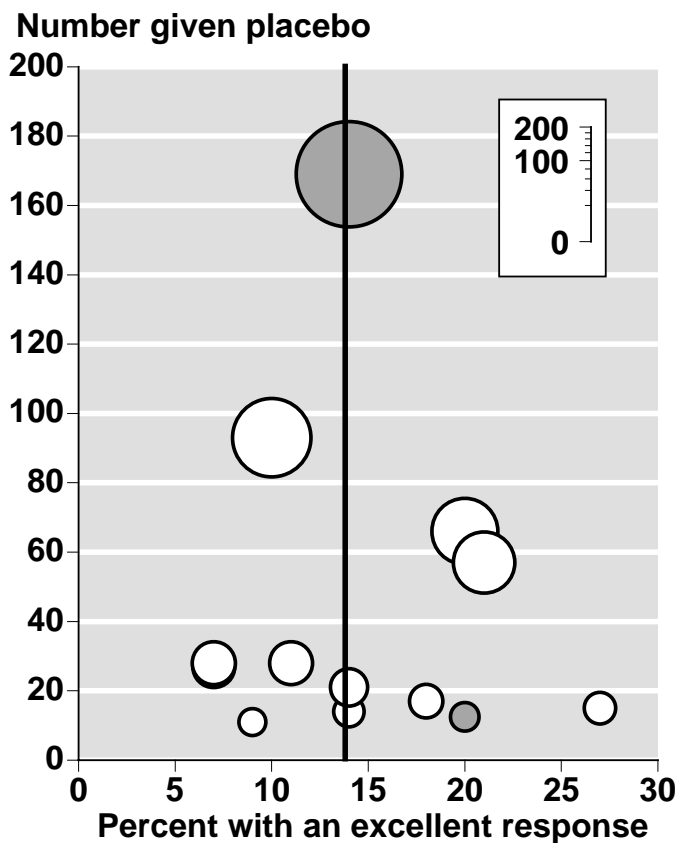


Figure 4: Placebo response rates in individual trials with cisapride with good or excellent symptom improvement. Shaded symbols are open studies.

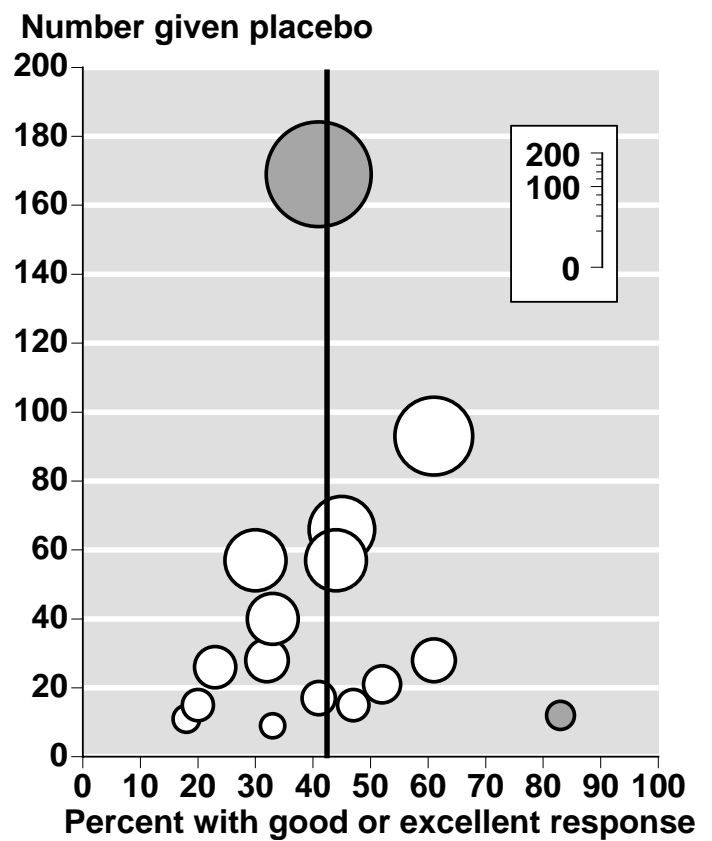


Figure 5: Cisapride response rates in individual trials with cisapride with excellent symptom improvement. Shaded symbols are open studies.

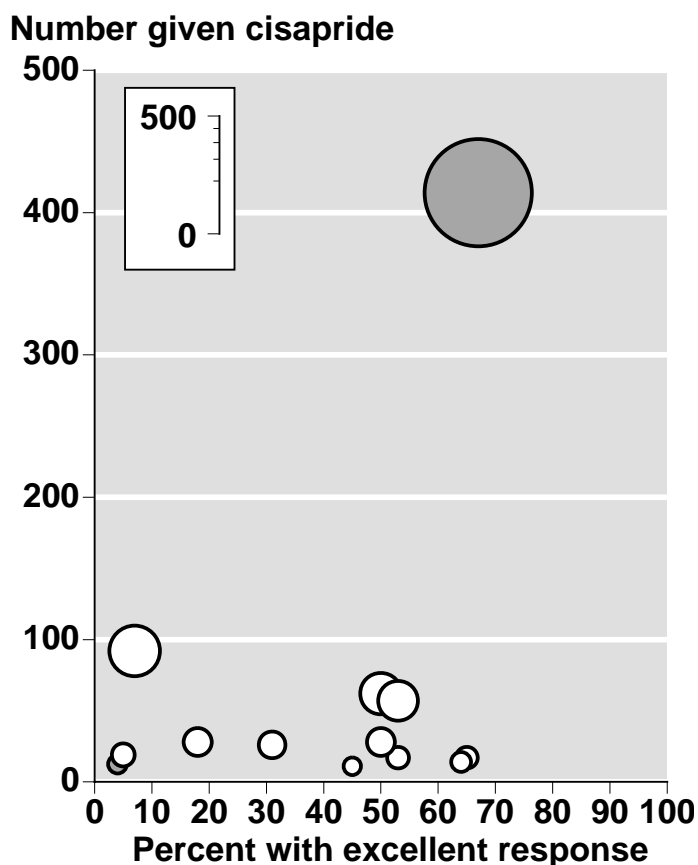
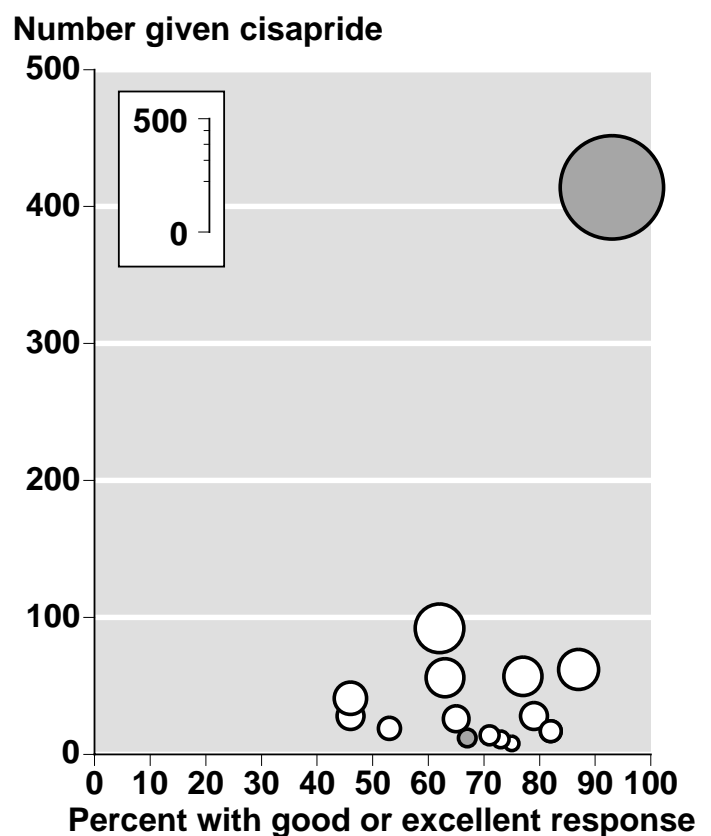


Figure 6: Cisapride response rates in individual trials with cisapride with good or excellent symptom improvement. Shaded symbols are open studies.



196/257 (76%) patients had good or excellent response with cisapride compared with 169/269 (63%) with histamine antagonist. The NNT was 7.4 (4.7 to 18).

Comment

The clinical picture

This review could be taken as confirmation that cisapride is moderately effective in symptom relief over about four weeks in patients given a dose of about 30 mg a day. For every four or five patients treated with cisapride, one will have good and / or excellent symptom relief who would not have benefited with placebo. Thirty-five percent (95% confidence interval 30%-40%) of patients will have an excellent response and 68% (64%-72%) will have a good or excellent response.

The fact that cisapride was more effective than histamine antagonists is useful supporting data. There are problems. Non-ulcer dyspepsia was defined endoscopically, and this limits the usefulness of the results in primary care. We would benefit from better diagnostic criteria.

Variation in placebo effects

In *Bandolier* 72 we looked at variation in endoscopic healing rates in reflux oesophagitis with placebo, but failed to make the link between the estimate of effect with placebo and the size of the sample. Figure 2 shows the placebo response for the excellent outcome in individual trials, and Figure 3 the placebo response for good or excellent outcome (but note that the X-axis is different for the two graphs).

There are two observations. More patients achieve the lower hurdle of good or excellent (mean 43%; 95% CI 37%-52%) than achieve the higher hurdle of an excellent response (mean 14%; 95% CI 11%-17%). Responses to placebo are the same for double blind and open studies (Table 1).

In both there is large variability at low sample size. For an excellent response the range is 7% to 27%, and for a good or excellent response it is 18% to 83%. Almost all of this variation is, as expected, with the smallest studies with sample sizes of 30 patients or fewer. Larger samples are less inaccurate.

Variation in cisapride effects

Figures 3 and 4 show the individual trial responses to cisapride for an excellent and a good or excellent response, respectively. Again there is considerable variation. But now the response for the open studies is considerably different from that for the double blind studies. Influenced mainly by one large open study, the cisapride response is much higher (see also Table 1).

Use of open studies

Bandolier has reported before that double blind studies produce lower treatment effects than open studies. Open studies are biased, and here we have a beautiful example of

how a single, large, study can overwhelm several smaller studies with more robust design. One doesn't need statistics to show it, it is there in the graphs. The lesson keeps being learned: beware including studies of inadequate design.

Reference:

- 1 VK Shukla, N Otten, C Dubé, D Moher. Use of cisapride in patients with non-ulcer dyspepsia: a meta-analysis of randomized trials. Ottawa: Canadian Coordinating Office for Health Technology Assessment (CCOHTA); 2000.

BOOK REVIEWS

Rational diagnosis and treatment: evidence-based clinical decision making. HR Wulff & PC Gøtzsche. Blackwell Science, Oxford. 3rd edition. 221pp. ISBN 0-632-03197-2

This is a terrific book concerning some of the fundamental concepts of clinical decision making. It has a distinctly philosophical bent, yet at the same time is an easy, interesting and instructive read. It has some history, which *Bandolier* enjoys.

Most importantly, whenever it touches on a topic there are wise words. Some of the comments on clinical and laboratory measurement, on numbers, and on descriptions of diagnostic tests really hit the spot.

Perhaps the best accolade *Bandolier* can give it is this: it goes into our holiday reading pile, because we want to read it again, more slowly, and more thoughtfully. It isn't a text book to be picked at when you have a problem, but a book that can redefine the way you think about things.

Evidence-based practice: a primer for health care professionals. M Dawes et al. Churchill Livingstone, Edinburgh, 2000. 254pp. ISBN 0-443-06126-2

Primer: an elementary introduction to any subject. For people who want a gentle introduction to the concepts and practice of EBM, this is the book for them. The language is clear. The topics covered are relevant, and range from critical appraisal, searching, study architecture, clinical guidelines, health economics and teaching. It was written to accompany the Master's course in evidence-based health care at the University of Oxford, and its clarity reflects the tempering process of the classroom.

Some parts are invaluable. Robin Snowball's collection of the best sources of information about EBM alone make the book worth having, with 11 pages of sources of information in paper, on CD-ROM, and on the Internet. A good book this for students, and for those of us still trying to get to grips with EBM in the practice, or on the ward, or in the office.

USE OF PARACETAMOL IN RHEUMATIC DISEASE

Bandolier has long been encouraged by readers to find evidence that paracetamol is the best thing since sliced bread for arthritic and rheumatic conditions, or that it does not work in these same conditions. There are some strong views, but very little hard evidence from randomised trials that helps. What do patients think? A survey of patients with rheumatoid arthritis, osteoarthritis and fibromyalgia may help [1].

Study

As part of a long term prospective study going on since 1974, 2,085 participants were mailed a six-monthly questionnaire. All had clinically defined rheumatoid arthritis, osteoarthritis or fibromyalgia. In July 1998 four additional questions were asked about the use of paracetamol. These addressed use of paracetamol, effectiveness of paracetamol, effectiveness compared with NSAIDs and satisfaction compared with NSAIDs considering both effectiveness and adverse effects.

Results

The questionnaire was returned by 1,799 patients (86%), of whom 1,187 had taken paracetamol. There were 825 responders with rheumatoid arthritis, 668 with osteoarthritis and 286 with fibromyalgia.

Of those who had taken paracetamol, 37% had found it moderately or very effective and 63% found slight or no effective (Figure 1). Responses on questions of efficacy and satisfaction compared with NSAIDs were similar. About 60% found paracetamol less effective or satisfactory than NSAIDs, 25% found it about the same, and 13% found it more effective or satisfactory (Figures 2 and 3).

Comment

There were minor differences between responders and non-responders in the survey, and minor differences between disease states and with age, but none of any obvious importance. Obviously this is much less satisfactory than a properly conducted, large, long term randomised trial. But in the absence of those, what this does is to confirm our prejudices.

It demonstrates that for a significant minority of patients paracetamol can be effective, and given the cost and safety issues, it is reasonable as a first choice, or as an addition to NSAIDs. It also shows that for many patients it simply isn't good enough, and that patients may not be best served by persevering with an ineffective medicine.

Reference:

- 1 F Wolfe, S Zhao, N Lane. Preference for nonsteroidal antiinflammatory drugs over acetaminophen by rheumatic disease patients. *Arthritis & Rheumatism* 2000 43: 378-385.

Figure 1: How 1,187 patients rated the effectiveness of paracetamol

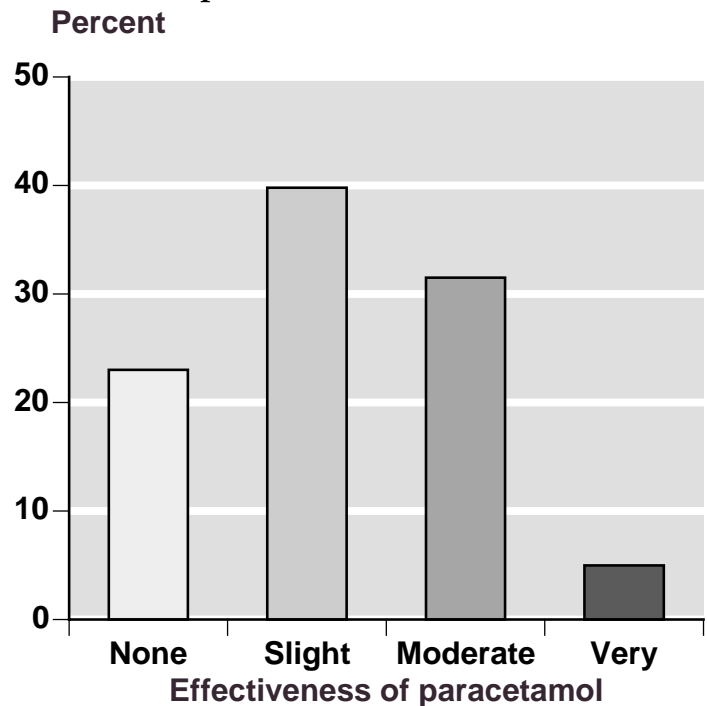


Figure 2: How patients rated effectiveness of paracetamol compared with NSAIDs

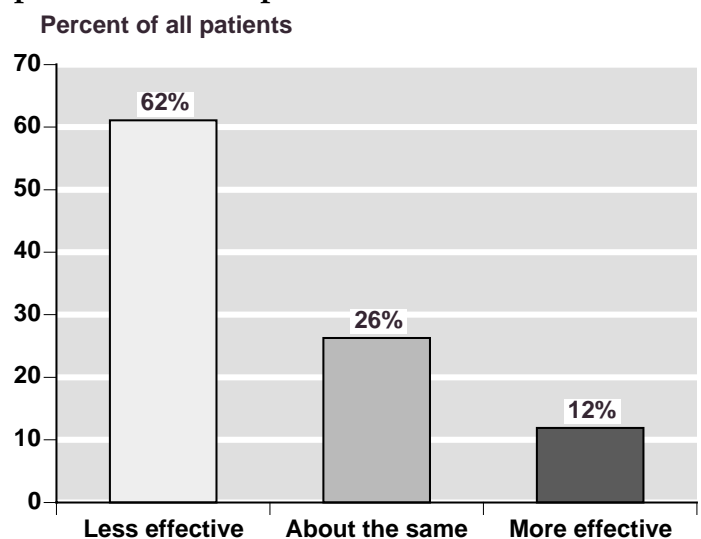
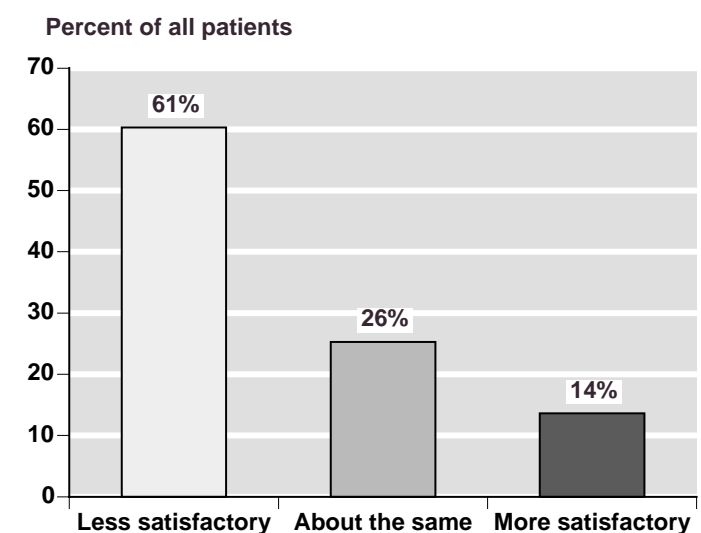


Figure 3: How patients rated effectiveness and adverse effects of paracetamol compared with NSAIDs



BREAST IMPLANTS AND CONNECTIVE TISSUE DISEASE

Bandolier 74 featured a formal risk assessment of silicone breast implants, but bemoaned the fact that the review did not state that it was systematic. Then, just like the proverbial buses, along comes a superb meta-analysis investigating the risk of connective tissue disorders in women with breast implants [1].

Search

Searching four electronic databases augmented publications identified by previous meta-analyses. Cohort, case-control and cross sectional studies were sought. Disease variables were presence or absence of individual connective tissue disease, of all connective tissue diseases combined, or of other autoimmune or connective tissue diseases. Presence or absence of any breast implant or implants described as silicone gel filled implants was noted.

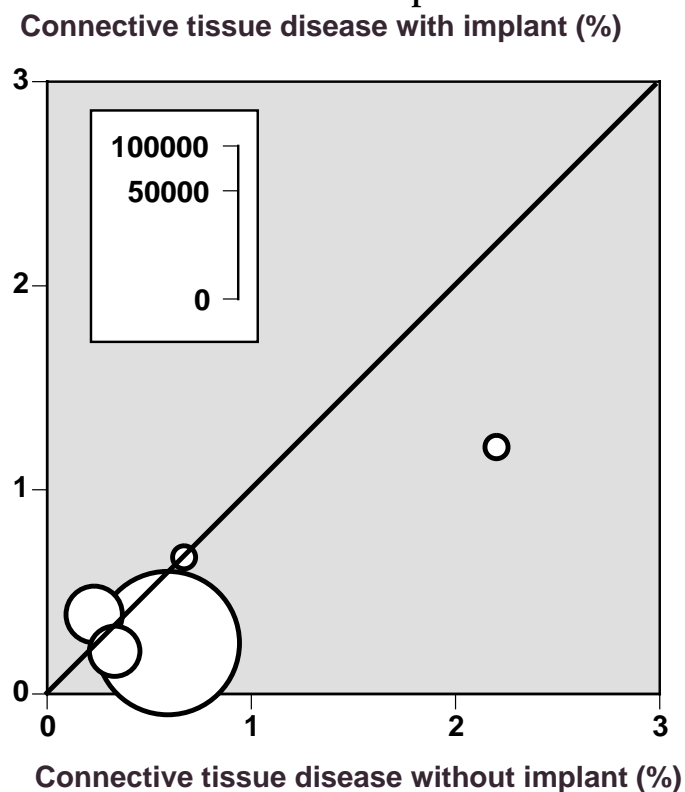
Results

There were nine cohort studies with 14,500 women with implants and 103,000 women without implants, nine case control studies with over 3000 women with disease and over 11,000 women without disease, and two cross sectional studies, one of which was very large with nearly 400,000 women. This large study used self-reported disease status, rather than a review of medical records to confirm disease, and was subject to other methodological problems.

There was little or no evidence of any association between breast implants and connective tissue disease. In the cohort studies, for instance, five studies had the outcomes of definite or any connective tissue disease. In women with breast implants, 53 of 13520 women (0.39%, 95% confidence interval 0.29%-0.50%) had this outcome, while 575 of 102,917 (0.56%, 95% confidence interval 0.51%-0.60%) of women without implants had the outcome (Figure).

There were several ways of looking at the results, including whether the relative risks were adjusted or not, and whether the very large cross sectional study was included

Figure: Connective tissue disease in women with and without breast implants



or not. The most conservative way of looking at the results, using adjusted relative risks (Table) showed no increased risk for all breast implants or for those with silicone gel fill.

Comment

This study is interesting in that it formed part of a report from a science panel appointed by a US judge to examine the scientific evidence for a case involving harm caused by breast implants. It is difficult, on this evidence, to implicate breast implants, silicone filled or not, in development of connective tissue disorders in women.

Reference:

- 1 EC Janowsky, LL Kupper, BS Hulka. Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. *New England Journal of Medicine* 2000 342: 781-790.

Table: Adjusted relative risks for connective tissue diseases in women with any breast implant and for those definitely identified as silicone gel filled implants

Disease	All breast implants		Silicone breast implants	
	Number of studies	Relative risk (95% CI)	Number of studies	Relative risk (95% CI)
All connective tissue diseases	13	0.80 (0.62 to 1.04)	6	0.82 (0.46 to 1.46)
Rheumatoid arthritis	7	1.04 (0.72 to 1.51)	3	0.98 (0.40 to 2.37)
Systemic lupus erythematosus	4	0.65 (0.35 to 1.23)	1	0.94 (0.17 to 5.23)
Scleroderma or systemic sclerosis	4	1.01 (0.59 to 1.73)	3	0.85 (0.32 to 2.25)
Sjögren's syndrome	3	1.42 (0.65 to 3.11)	1	0.99 (0.17 to 5.94)
Other autoimmune or rheumatic conditions	6	0.96 (0.74 to 1.25)	2	0.61(0.41 to 0.91)

Adjusted relative risks. Significant increase in connective tissue disease in women with breast implants would be shown by a lower limit of the confidence interval greater than 1.

NABUMETONE & MELOXICAM

GASTROINTESTINAL SAFETY

The increasing focus on serious gastrointestinal adverse effects of NSAIDs is resulting in more information becoming available. Two new meta-analyses concentrate on nabumetone [1] and meloxicam [2].

Nabumetone search

Data on randomised controlled comparisons with NSAIDs in patients with osteo- or rheumatoid arthritis was sought, together with postmarketing, open, or extended studies. They had to be on adults and only the English language literature was searched.

Outcome

The major outcome sought was perforation, ulcer, or bleed (PUB). Only patients with haematemesis or haematochezia were included, and not those with positive stool tests with no other confirmation.

Results

The relevant results were from eight comparative studies in which nabumetone was compared with NSAID over periods from 1.5 to six months. The overall incidence of PUBs with nabumetone was 3 in 4,847 patients (0.06%) compared with 24 of 2,621 patients (0.9%). The analysis by patient years (Table) shows a slightly more flattering picture because two of the three bleeds with nabumetone occurred in studies in which the exposure could not be estimated.

Meloxicam search

A MEDLINE search for English language studies was augmented by hand searching US gastroenterology proceedings. No unpublished information was sought. The outcome of PUB was defined as gastric perforation, endoscopic ulcer in a patient with dyspepsia or abdominal pain, and/or gastrointestinal bleeding.

Results

Data from six studies with 19,331 patients in total were analysed, with meloxicam doses of 7.5 mg or 15 mg a day, over periods of 4-24 weeks (for most patients it was four weeks). The comparison was with NSAIDs at standard doses. Actual data are not given, but the summary odds ratio was 0.52 (95%CI 0.28 to 0.96).

Table: PUB events with nabumetone and NSAIDs

Treatment	Patient years exposure	Number of patients	Number with PUB	Percent per 100 patient years over 3-months
Nabumetone	1147	4098	1	0.09
NSAID	590	1874	17	2.9

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Comment

It is interesting to compare these meta-analyses with those done for trials with rofecoxib [3], with similar numbers of patients on NSAIDs and with similar mean duration of exposure (0.3-0.4 years). In the both the crude rate of PUBs with NSAIDs was about 1% (0.9% in nabumetone studies, 1% in rofecoxib studies). It was unfortunate that the meloxicam review did not give event rates, because the definition of PUB (including endoscopically diagnosed ulcer in a patient with dyspepsia or abdominal pain) may have been different, and the event rates would show this.

The crude estimates of PUB rates for both placebo and rofecoxib were about 0.6%. For nabumetone it was only a tenth of this, at 0.06%. This difference is not easily explained by obvious differences in patient populations, as both studies involved patients with osteoarthritis and/or rheumatoid arthritis with apparently similar ages. Inclusion criteria, or definition of PUB, which was not specific for nabumetone, might provide an answer. The most likely reason for any differences, though, is probably in the very small numbers of events.

On limited data, nabumetone seems safer than classical NSAIDs. On meloxicam there is insufficient evidence to make a judgement from the meta-analysis.

Reference:

- 1 J-Q Huang, S Sridhar, RH Hunt. Gastrointestinal safety profile of nabumetone: a meta-analysis. American Journal of Medicine 1999 107 (6A): 55S-64S.
- 2 P Schoenfeld. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials. American Journal of Medicine 1999 107: 48S-54S.
- 3 MJ Langman et al. Adverse upper gastrointestinal effects of rofecoxib compared with NSAIDs. JAMA 1999 282: 1929-1938.